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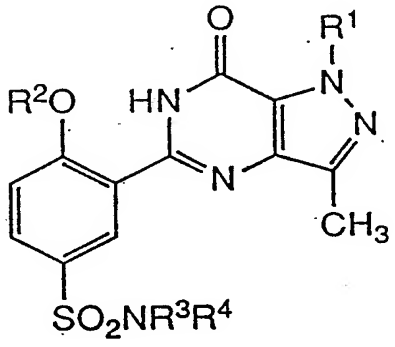
(54) Title: PYRAZOLOPYRIMIDINONE ANTIANGINAL AGENTS



(I)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein R^1 is methyl or ethyl; R^2 is ethyl or n-propyl; and R^3 and R^4 are each independently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino; are selective cGMP PDE inhibitors useful in the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

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PYRAZOLOPYRIMIDINONE ANTIANGINAL AGENTS

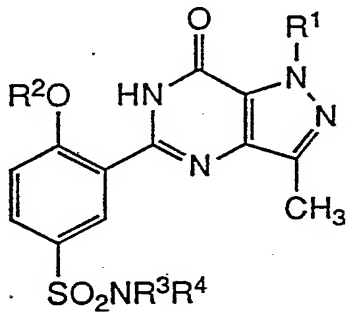
This invention relates to a group of pyrazolo[4,3-d]-pyrimidin-7-ones, which are potent and selective inhibitors of cyclic guanosine 3′, 5′-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3′,5′-monophosphate phospodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Certain pyrazolo[4,3-d]pyrimidin-7-ones are disclosed in European patent application EP-A-0201188, where they are described as adenosine receptor antagonists and PDE inhibitors, useful in the treatment of cardiovascular disorders such as heart failure or cardiac insufficiency. However the compounds specifically exemplified therein are neither particularly potent PDE inhibitors, nor are they claimed to be selective inhibitors of cGMP PDE.

It has now been discovered that 1,3-dialkyl-5-(disubstituted phenyl)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-ones, in which the two phenyl substituents are in a 2,5 relative disposition, possess unexpectedly high levels of both cGMP PDE inhibitory potency and, as stated above, selectivity for inhibition of cGMP PDEs over that of cAMP PDEs. These compounds are neither specifically disclosed nor exemplified in EP-A-0201188.

The compounds of the present invention have the formula (I):



(I)

wherein R^1 is methyl or ethyl;

R^2 is ethyl or n-propyl;

and R^3 and R^4 are each independently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino;

and pharmaceutically acceptable salts thereof.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight chain or branched chain. Thus the compounds of formula (I) may contain one or more asymmetric centres and consequently can exist as enantiomers or diastereoisomers; the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

Also included in the invention are radiolabelled

derivatives of compounds of formula (I) which are suitable for biological studies.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, furmarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^3 is H, methyl or ethyl; R^4 is C_1-C_6 alkyl optionally substituted with cyclohexyl or with morpholino; and R^1 and R^2 are as previously defined.

Particularly preferred individual compounds of the invention are:

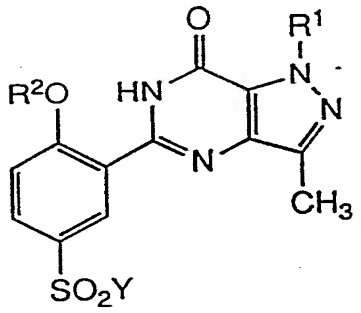
5-[2-ethoxy-5-(3-morpholinopropylsulphamoyl)-phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

and 5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of formula (I) may be prepared by the reaction of a compound of formula (II):



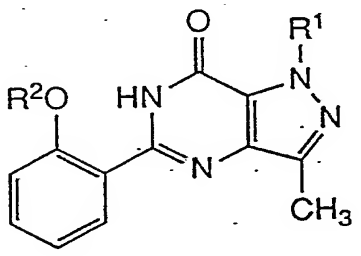
(II)

wherein R^1 and R^2 are as previously defined and Y is fluoro, chloro or bromo, preferably chloro, with a compound of formula (III):

$$HNR^3R^4 \quad \text{(III)}$$

wherein R^3 and R^4 are as previously defined.
The reaction is generally carried out at room temperature, preferably in the presence of a solvent, for example a C_1-C_3 alkanol, using an excess of (III) to scavenge the acid by-product (HY).

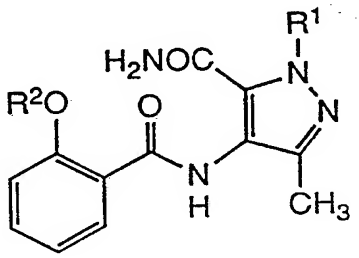
Compounds of formula (II) may be prepared from compounds of formula (IV):



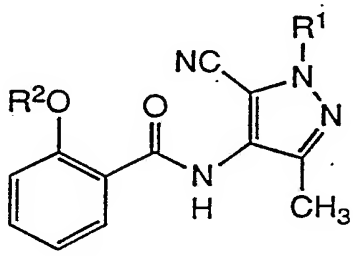
(IV)

wherein R^1 and R^2 are as previously defined, by the application of known methods for the introduction of a SO_2Y group, wherein Y is as previously defined, into an aromatic ring; for example, when Y is chloro, by the action of chlorosulphonic acid at or near 0°C.

Compounds of formula (IV) may be prepared from compounds of formula (V):



(V)



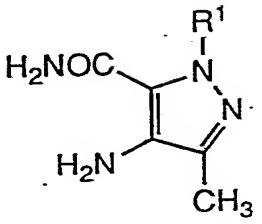
(VI)

wherein R^1 and R^2 are as previously defined, by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, the cyclisation may be effected by the treatment of (V) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide, in an ethanol-water medium at reflux temperature for 2-40 hours. Under these conditions the related nitrile of formula (VI), wherein R^1 and R^2 are as previously defined, may also be employed as the precursor to (IV).

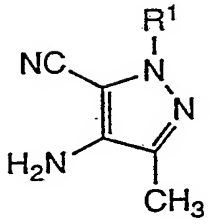
In an alternative cyclisation procedure, compounds of formula (IV) may be obtained by treatment of (V) with polyphosphoric acid at or near 140°C for 6-18 hours.

Compounds of formulae (V) and (VI) may be prepared

from compounds of formulae (VII) and (VIII) respectively:

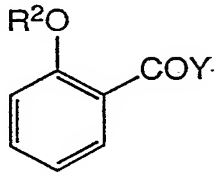


(VII)



(VIII)

wherein R^1 is as previously defined, by reaction with a compound of general formula (IX):



(IX)

wherein R^2 and Y are as previously defined.

The reaction is generally carried out using an excess of (IX) in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in an inert solvent such as dichloromethane at from about 0 to 25°C for 2-6 hours. For convenience, pyridine may also be used as co-solvent.

The amines of formula (III), the aminopyrazoles of formulae (VII) and (VIII), the acyl halides of formula (IX), and the various reagents required for the process hereinbefore disclosed, when neither commercially available nor subsequently described, can be obtained by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may also be prepared in a conventional manner. For example a solution of the free base is treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

All of the above reactions are entirely conventional and the necessary reagents and conditions for their performance can readily be established by reference to standard textbooks and to the Examples and Preparations provided hereafter. Alternatives and variations will also be evident to persons skilled in the art to enable all the compounds defined by formula (I) to be prepared.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their IC_{50} values (the

concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W. J. Thompson et al. (Biochem., 1971, 10, 311). The calcium/calmodulin (Ca/CAM)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of W. J. Thompson and M. M. Appleman (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs.

Platelet anti-aggregatory activity

This is assessed by the determination of a compound's ability to inhibit platelet aggregation in vitro induced by platelet activating factor (PAF), and to potentiate the platelet antiaggregatory action in vitro of activators of guanylate cyclase such as nitroprusside and EDRF. Washed platelets are prepared essentially by the method of J. F. Mustard et al. (Methods in Enzymol., 1989, 169, 3) and aggregation is determined using standard turbidimetric techniques as described by G. V. R. Born, (J. Physiol. (Lond), 1962, 162, 67P).

Antihypertensive activity

This is assessed following intravenous or oral administration of a compound to spontaneously hypertensive rats. Blood pressure is recorded via a cannula implanted in the carotid artery of either conscious or anaesthetised animals.

For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily

for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. The compounds may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with

a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for use in medicine.

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS.

In a further aspect, the invention provides a method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel potency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS, in a mammal (including a human being) which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

The invention also includes any novel intermediates of formulae (II) and (IV) disclosed herein.

The syntheses of the compounds of the invention and of the intermediates for use therein are

illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (tlc) using Merck Kieselgel 60 F_{254} plates. ^{1}H-Nuclear magnetic resonance spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

5-[2-Ethoxy-5-(3-morpholinopropylsulphamoyl)phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

N-(3-Aminopropyl)morpholine (0.943 g, 0.0066 mol) was added dropwise to a stirred suspension of 5-(5-chlorosulphonyl-2-ethoxyphenyl)-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.626 g, 0.00164 mol) in ethanol (40 ml). After 1 hour at room temperature, when tlc analysis showed no remaining starting material, the solvent was removed by evaporation under vacuum. The residue was partitioned between saturated aqueous sodium bicarbonate solution (30 ml) and dichloromethane (30 ml), then the organic phase removed and the aqueous phase further extracted with dichloromethane (3 x 30 ml). The combined organic solutions were dried (Na_2SO_4) and the solvent removed by evaporation under vacuum. The residue was purified by column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) followed by crystallisation of the resulting solid from ethyl acetate-methanol, to afford the title compound as white crystals (0.568 g, 73%), m.p. 193-195°C. Found: C,54.05; H,6.00; N,17.18. $C_{22}H_{30}N_6O_5S$ requires C,53.86; H,6.16; N,17.13%.

EXAMPLE 2

1-Ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxyphenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Following the procedure of Example 1, the title compound was prepared from 5-(5-chlorosulphonyl-2-n-propoxyphenyl)-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0012 mol) and hexylamine (0.49 g, 0.0048 mol). After crystallisation from EtOAc-hexane, the product was obtained as a white solid (0.328 g, 57%), m.p. 172-174°C. Found: C,58.02;

H,6.98; N,14.85. $C_{23}H_{33}N_5O_4S$ requires C,58.08; H,6.99; N,14.73%.

EXAMPLE 3

5-[5-(N-Cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Following the procedure of Example 1, the title compound was prepared from 5-(5-chlorosulphonyl-2-n-propoxyphenyl)-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.7 g, 0.0017 mol) and N-methylcyclohexylmethylamine (0.433 g, 0.0034 mol) (prepared by borane:dimethylsulphide mediated reduction of N-formylcyclohexylmethylamine). After crystallisation from EtOAc-hexane, the product was obtained as colourless crystals (0.668 g, 78%), m.p. 190-192°C. Found: C,60.03; H,7.07; N,13.96. $C_{25}H_{35}N_5O_4S$ requires C,59.86; H,7.03; N,13.96%.

EXAMPLE 4

1-Ethyl-5-(5-diethylsulphamoyl-2-n-propoxyphenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Following the procedure of Example 1, the title compound was prepared from 5-(5-chlorosulphonyl-2-n-propoxyphenyl)-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0012 mol) and diethylamine (0.5 ml, 0.356 g, 0.0048 mol). After crystallisation from EtOAc-hexane, the product was obtained as white crystals (0.379 g, 70%), m.p. 181-183°C. Found: C,56.47; H,6.42; N,15.62. $C_{21}H_{29}N_5O_4S$ requires C,56.36; H,6.53; N,15.65%.

PREPARATION 1

4-(2-Ethoxybenzamido)-1,3-dimethylpyrazole-5-carboxamide

A solution of 2-ethoxybenzoyl chloride (14.42 g, 0.078 mol) in dichloromethane (50 ml) was added dropwise to a stirred solution of 4-amino-1,3-dimethylpyrazole-5-carboxamide (12.0 g, 0.078 mol) (prepared by the method of J. Med. Chem., 1987, 30, 91 in pyridine (150 ml) and the resulting mixture stirred at room temperature overnight in a dry nitrogen atmosphere. The solvent was removed by evaporation under vacuum and the residue partitioned between ethyl acetate (100 ml) and saturated aqueous sodium carbonate solution (100 ml). The organic phase was separated and the aqueous phase exhaustively extracted with ethyl acetate. The combined organic solutions were dried (Na_2SO_4) and evaporated under vacuum. The solid thus obtained was triturated with diethyl ether (100 ml), then dried, to give the product as a white solid (19.24 g, 82%), m.p. (after crystallisation from ethyl acetate) 178-181°C. Found: C,59.89; H,6.05; N,18.44. $C_{15}H_{18}N_4O_3$ requires C,59.59; H,6.00; N,18.53%.

PREPARATION 2

5-(2-Ethoxyphenyl)-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

4-(2-Ethoxybenzamido)-1,3-dimethylpyrazole-5-carboxamide (1.6 g, 0.0053 mol) was added to polyphosphoric acid (50 g) and the mixture heated at about 140°C for 6 hours. The cool reaction mixture was poured onto ice/water (100 g), then the resulting solution basified with 10% aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum to give the crude product. After purification by column chromatography (SiO_2, 3%

MeOH in CH_2Cl_2), followed by crystallisation from aqueous ethanol, the title compound was obtained as colourless crystals (0.26 g, 17%), m.p. 201-204°C. Found: C,63.43; H,5.57; N,19.35. $C_{15}H_{16}N_4O_2$ requires C,63.36; H,5.67; N,19.71%.

PREPARATION 3

5-(5-Chlorosulphonyl-2-ethoxyphenyl)-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5-(2-Ethoxyphenyl)-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.0 g, 0.0032 mol) was added portionwise to cold (0°C) chlorosulphonic acid (6 ml) and the resulting solution stirred at room temperature for 12 hours. The reaction mixture was added dropwise to ice/water (50 g) and the resulting aqueous solution extracted with dichloromethane (4 x 50 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed by evaporation under vacuum to give a white solid which, on trituration with diethyl ether provided the title compound (1.21 g, 100%), m.p. 233-235°C. Found: C,47.24; H,3.73; N,14.54. $C_{15}H_{15}ClN_4O_4S$ requires C,47.06; H,3.95; N,14.64%.

PREPARATION 4

1-Ethyl-3-methyl-4-(2-n-propoxybenzamido)pyrazole-5-carboxamide

Following the procedure of Preparation 1, the title compound was prepared from 2-n-propoxybenzoyl chloride (2.16 g, 0.0109 mol) and 4-amino-1-ethyl-3-methylpyrazole-5-carboxamide (0.916 g, 0.0055 mol) (prepared by the method of EP-A-0095289). The product was obtained as a white solid (1.63 g, 91%), m.p. (after crystallisation from ethyl acetate-hexane) 150-152°C. Found: C,61.87; H,6.46; N,17.16. $C_{17}H_{22}N_4O_3$ requires C,61.80; H,6.71; N,16.96%.

PREPARATION 5

1-Ethyl-3-methyl-5-(2-n-propoxyphenyl)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

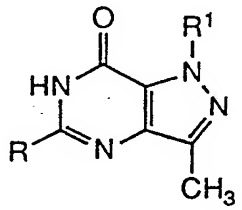
1-Ethyl-3-methyl-4-(2-n-propoxybenzamido)pyrazole-5-carboxamide (8.0 g, 0.024 mol) was added to a stirred solution of sodium hydroxide (4.84 g, 0.121 mol) in water (180 ml) and ethanol (50 ml) and the mixture heated under reflux for 12 hours. The solution was allowed to cool and extracted with dichloromethane (6 x 60 ml); the combined extracts were then dried (Na_2SO_4) and the solvent removed by evaporation under vacuum. Crystallisation of the resulting solid from EtOAc-hexane gave the title compound as white crystals (5.0 g, 66%), m.p. 149-151°C. Found: C,65.53; H,6.59; N,18.02. $C_{17}H_{20}N_4O_2$ requires C,65.37; H,6.45; N,17.94%.

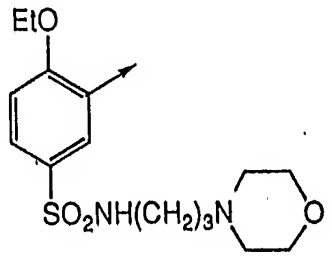
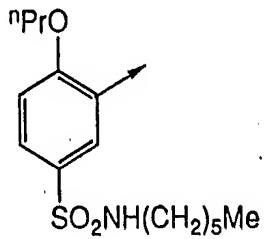
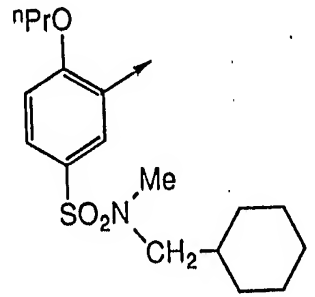
PREPARATION 6

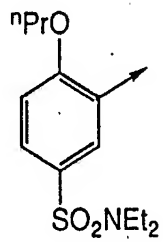
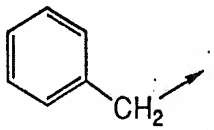
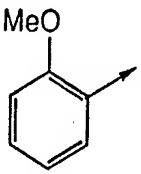
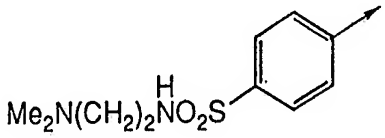
5-(5-Chlorosulphonyl-2-n-propoxyphenyl)-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Following the procedure of Preparation 3, the title compound was prepared from 1-ethyl-3-methyl-5-(2-n-propoxyphenyl)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (2.5 g, 0.008 mol) and chlorosulphonic acid (8 ml). The product was obtained as a white solid (3.17 g, 96%), m.p. 155-158°C. Found: C,49.19; H,4.50; N,13.38. $C_{17}H_{19}ClN_4O_4S$ requires C,49.70; H,4.66; N,13.64%.

In vitro inhibitory activity and selectivity against the Ca/CAM-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes

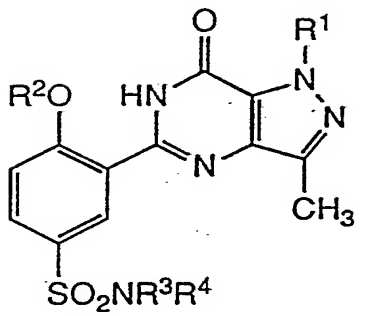


COMPOUND REFERENCE	R	R^1	IC_{50} (μM) v. cGMP PDE	IC_{50} (μM) v. cAMP PDE	SELECT-IVITY RATIO
Example 1		Me	0.13	~ 10	~ 769
Example 2		Et	0.0048	11	2292
Example 3		Et	0.0048	1.2	250

Example 4		Et	0.0047	18	3830
Example 1 of EP-A-0201188		Me	4.7	98.7	21
Example 14 of EP-A-0201188		Me	4.0	72	18
Example 21 of EP-A-0201188		Me	>10	>10	-

CLAIMS

1. A compound of formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is methyl or ethyl;

R^2 is ethyl or n-propyl;

and R^3 and R^4 are each indepdendently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino.

2. A compound as claimed in claim 1 wherein R^3 is H, methyl or ethyl; and R^4 is C_1-C_6 alkyl optionally substituted with cyclohexyl or with morpholino.

3. A compound as claimed in claim 2 wherein the said compound is selected from:

5-[2-ethoxy-5-(3-morpholinopropylsulphamoyl)-phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

and 5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

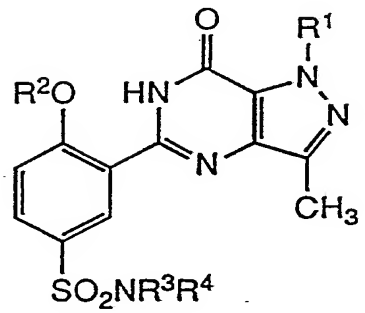
4. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, together with a pharmaceutically acceptable diluent or carrier.

5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4, for use in medicine.

6. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

7. A method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a mammal (including a human being), which comprises administering to said mammal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4.

8. A process for the preparation of a compound of formula:



(I)

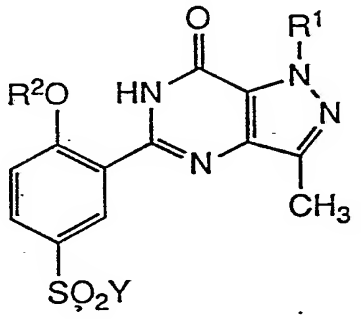
or a pharmaceutically acceptable salt thereof,

wherein R^1 is methyl or ethyl;

R^2 is ethyl or n-propyl;

and R^3 and R^4 are each independently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino;

which comprises reacting a compound of formula:



(II)

wherein Y is fluoro, chloro or bromo, and R^1 and R^2 are as previously defined in this claim, with a compound of formula:

HNR^3R^4 (III)

wherein R^3 and R^4 are as previously defined in this claim, followed by optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

9. A process as claimed in claim 8 wherein R^3 is H, methyl or ethyl; and R^4 is C_1-C_6 alkyl optionally substituted with cyclohexyl or with morpholino.

10. A process as claimed in claim 9 wherein the said compound of formula (I) produced is selected from:

5-[2-ethoxy-5-(3-morpholinopropylsulphamoyl)-phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

and 5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

11. A process as claimed in any one of claims 8 to 10 wherein Y is chloro.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/02068

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; A61K31/505; //(C07D487/04,239:00,231:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 201 188 (WARNER-LAMBERT) 17 December 1986 cited in the application see claims 1,9	1,4
P,A	EP,A,0 463 756 (PFIZER) 2 January 1992 see claims 1,7	1,4

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 DECEMBER 1992	23. 12. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9202068 SA 64107

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/12/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0201188	12-11-86	US-A- 4666908	19-05-87
		JP-A- 61236778	22-10-86
EP-A-0463756	02-01-92	AU-B- 626757	06-08-92
		AU-A- 7915591	19-03-92
		CN-A- 1057464	01-01-92